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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SAKELARIS, SALLY A	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 12/21/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/744,373	KIMBERLY, ROBERT P.	
	Examiner	Art Unit	
	Sally A Sakelaris	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 September 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21,26-30,34 and 36-46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-21, 26-30, 34, and 36-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This action is written in response to applicant's correspondence submitted 9/24/2004. Claims 1, 13, 21, 34, 36, and 42-46 have been amended, claims 31-33 and 35 have been canceled, claims 22-25 have been withdrawn from consideration and no claims have been added. Claims 1-21, 26-30, 34, and 36-46 are pending. Applicant's amendments and arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections not reiterated in this action have been withdrawn as necessitated by applicant's amendments to the claims. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. **This action is FINAL.**

Declaration

The Declaration under 37 CFR 1.132 filed 9/24/2004 is insufficient to overcome the rejection of claims 1-21, 26-30, 34, and 36-46 based upon 112 1st paragraph as set forth in the last Office action because: applicant has shown that their specification has only enabled a scope of their newly amended invention(see below new rejection under 112 1st paragraph). Furthermore, it is noted that it is not clear what relevance the data on pages 4-8 and table 1 has considering the lack of p-values, or other means for showing statistical significance. It should be further noted that in the case applicant should re-submit a declaration in the future prosecution of this application, they have a hand-delivered copy sent to the examiner to insure legibility of the paper.

Response to Arguments

Applicant's arguments with respect to claim1-21, 26-30, 34, and 36-46 have been considered but are moot in view of the new grounds of rejection.

THE FOLLOWING ARE NEW GROUNDS OF REJECTION NECESSITATED BY APPLICANT'S AMENDMENTS TO THE CLAIMS

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

1. Claim 34 is rejected under 35 U.S.C. 103(a) as being unpatentable over Morton et al. (Immunogenetics 1996 43:246-247) in view of Ahern et al.(The Scientist, Vol. 9 #15, pg. 20, July 24, 1995).

Morton et al. teach the single nucleotide polymorphisms in FcalphaRI consisting of the silent SNP in codon 87(R), an Asp-Asn in codon 92(D-N), and a Phe-Leu at codon 132(F-L)(see also applicant's specification on page 24 lines 1-4).

However, Morton et al. do not teach one of the alleles selected from this group further comprising a commercial package, reagents, and instructions, Ahern et al. teach the many advantages associated with the use of a commercial package and/or a reagent kit, comprising reagents for the PCR based detection of polymorphisms and further teach the accompaniment of "detailed instructions to follow"(Page 4) and the expected benefit of "buying premade reagents and kits because they are convenient and they save time"(Page 4 second paragraph).

Therefore, It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to combine the SNPs of Morton et al. with kit of Ahern et al. for the expected benefit that while "premade biochemicals and reagents offer scientists the opportunity to better manage their time, putting these products all together in kits take the convenience one step further"(Page. 4, 1st paragraph).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claim 1-21, 26-30, 34, and 36-46 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

- Correlating a glycine at amino acid(AA) position 248 of CD89(or an A at nucleotide 844) with a functional capacity of initiating an greater intracellular calcium flux relative to the same of a serine at codon 248(or a G at nucleotide 844).
- Correlating a glycine at AA position 248 of CD89 with the release of more IL-6 and less TNFα upon binding stimulation of the CD89 receptor as compared to a like number of 844A(serine at 248) allele containing receptors.

But does not reasonably provide enablement for correlating any FcαRI induced function of a cell expressing FcαRI and cellular susceptibility to any disease by identifying a FcαRI genotype of said cell for FcαRI alleles selected from any of the group consisting of: FcαRIa 87R/87R, FcαRIA 92D/92N, FcαRIa 132F/132L, FcαRI 245P/245L and FcαRI 248S/248G. The

specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the specification coupled with information known in the art without undue experimentation (*United States v. Telectronics.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is needed is not based upon a single factor but rather is a conclusion reached by weighing many factors. These factors were outlined in *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and again in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988) and include the following:

Nature of the invention. Claims 1-21, 26-30, 34, and 36-46 are broadly drawn to methods of correlating any FcαRI induced function of a cell expressing FcαRI and cellular susceptibility to a disease. The newly submitted declaration exemplifying examples 17 and 25 of the specification only enables a Correlation of a glycine at AA position 248 of CD89(or an A at nucleotide 844) with a functional capacity of initiating an intracellular calcium flux greater relative to the serine at codon 248(or a G at nucleotide 844) and furthermore a glycine at AA position 248 of CD89 with the release of more IL-6 and less TNFα upon binding stimulation of the CD89 receptor as compared to a like number of 844A(serine at 248) allele containing receptors. The specification does not specify any examples of such well-established, *in–vitro* model systems or evidence for the ability of correlating any FcαRI induced function of a cell expressing FcαRI and cellular susceptibility to any disease by identifying a FcαRI genotype of said cell for FcαRI alleles selected from any of the group consisting of: FcαRIa 87R/87R, FcαRIA 92D/92N, FcαRIa 132F/132L, FcαRI 245P/245L and FcαRI 248S/248G and its predictable association with cellular

susceptibility to any disease. The examples that are taught in the specification include only SNPs in the coding regions of FcγRIIA, FcγRIIIA, and FcγRIIIB and a belief that a "precedent" is established by these findings, that these SNPs influence the risk for Periodontal Disease(PD). The specification continues on to conclude that the findings for one gene coding for the IgG receptor can be applicable to that of another gene coding for the different, IgA receptor. The specification teaches that the "knowledge that PD lesions are rich in both IgG and IgA."(Pg 23, line 20-23) is enough to lead one skilled in the art to believe that their receptors function exactly the same. The specification merely prophesizes that as a result of these previous findings with the IgG receptor, "the present invention identifies novel SNPs in FcαRI." It is highly unpredictable to extrapolate findings from the Fcγ molecules to the entirely different molecules defined by FcαRI. In addition, it is important to note that even if applicant would enable the detection of SNPs in the FcαRI gene, only those genotypes taught in the specification on Pg. 33 in example 3, would be enabled, not all genotypes of the receptor. Furthermore, this method includes i). identifying a FcαRI genotype from the group consisting of 87R/87R, FcαRIA 92D/92N, FcαRIa 132F/132L, FcαRI 245P/245L and FcαRI 248S/248G, ii). quantifying IgA binding by a cell with said genotype, and iii). comparing IgA binding by said cell and IgA binding by a second cell, said second cell expressing a second FcαRI genotype. Furthermore, while the method's step i), of identifying a genotype would include the "how to make" portion of the enablement requirement, it still omits the "how to use portion" as the specification omits any teaching of how to use the discovered genotype once it has been discovered. With respect to step ii), it is unclear how the amount of bound IgA relates to the genotype of a cell. The specification does not teach the effect that the amount of bound IgA has on the genotype of the cell or vice

versa. Lastly, as in steps i) and ii), the specification does not teach which genotype said first cell has nor what genotype said second cell has and why either of these would be significant as related to each cell's ability to bind IgA.

With respect to claim 34, although directed to a product, the reagents will be used to identify individual susceptibility to a disease, a feat that as previously mentioned lacks enablement because of the great unpredictability that exists in such a research project. The nature of this invention is quite unpredictable because it requires a reliance on the prophetic testimony by applicant that the progression of any disease will in fact be evident through the detection of any FcαRI genotype selected from the group consisting of 87R/87R, FcαRIA 92D/92N, FcαRIa 132F/132L, FcαRI 245P/245L and FcαRI 248S/248G.

Scope of the invention. The scope of the invention is very broad, claiming methods for correlating the FcαRI induced function of a cell expressing FcαRI and the cellular susceptibility to any disease. Much unpredictability exists in the broad claiming of any type of cell and having, as in steps i) ii) and iii)'s, any genotype selected from the group consisting of 87R/87R, FcαRIA 92D/92N, FcαRIa 132F/132L, FcαRI 245P/245L and FcαRI 248S/248G being correlated to any amount of bound IgA by the cell expressing said genotype. Furthermore, as eluded to in the Nature of the invention, even if applicants would enable detection of SNPs in the FcαRI gene, their scope would still be limited to those of examples 17 and 25 in the specification as validated by the declaration data and therefore only nucleotide 844G(Glycine at position 248).

State of the art. The prior art does not disclose a method for correlating the FcαRI induced function of a cell expressing FcαRI and the cellular susceptibility to any disease, thus the invention appears to be novel in terms of the prior art. However, the lack of support from the prior art for the ability of a genotype of the FcαRI, IgA receptor, to have such far-reaching

effects such as into the manifestation of any disease, results in the invention being unpredictable in terms of its use as presently claimed. Furthermore, as the present application relies on the extrapolation from data involving the receptor for the IgG molecule to define characteristics for the receptor of the IgA molecule, the art teaches great unpredictability associated with this practice. The specification's reliance on the IgG receptor data implies that IgG and IgA are identical. However, Morton et al. teach "the cDNA encoding the myeloid FcαR has been characterized and was found to encode a 30-kDa peptide with two extracellular Ig-like domains" the reference goes on to teach though that, "the gene structure indicates FcαR to represent a more distantly related member of the immunoglobulin receptor gene family." (JBC, 1995) Furthermore, Carayannopoulos et al. teach while the FcαR receptor "shows similarity to the high affinity FcεR and the three FcγR but is more distantly related to these receptors than they are to one another"(J. Exp. Med. 1996). In addition to the prior art, the post date art also teaches variation between these two receptor types. Wines et al teach that the "comparison of the FcγRI:IgA interaction showed considerable differences from the well-defined FcγR:IgG and FcεRI:IgE interactions. Unlike other Fc receptors, in FcαRI the ligand binding site appears to be in the first domain, not the second, and in IgA, unlike IgG or IgE, the receptor binding site is located at the interface between CH2 and CH3, not the lower hinge of CH2 as for IgG or its equivalent area in IgE Cε2."(AAI, 2001) Such variance between IgG receptors and those for IgA makes drawing conclusions and the subsequent extrapolations about the two molecules, highly unpredictable.

Furthermore, with respect to the applicant's assertion that their invention provides SNPs that "lead to coding changes in both the extracellular and cytoplasmic domains"(Spec. pg. 8) and that "the present invention uses a single nucleotide polymorphism or combinations thereof within a FcαRI genotype to identify individual susceptibility to a disease"(Pg. 9), the prior art does not provide any specific guidance with regard to the instantly claimed particular polymorphism located in FcαRI. There is a large body of knowledge in the prior art related to polymorphisms in general, and their association with diseases or disease states. The art is highly unpredictable with regard to the functionality of polymorphic sites in genomic DNA. After a screening assay identifies polymorphisms, it is unpredictable whether any such polymorphisms would be associated with any phenotypic trait, such as a disease state or a physiological state. For example,

Hacker et al. were unable to confirm an association between a gene polymorphism and ulcerative colitis in a case where prior studies suggested such a relationship would exist since the relationship had been identified in a different population (Gut, 1997, Vol. 40, pages 623-627). Even in cases where an association between a particular gene and a disease state is known to exist, such as with the LPL gene and heart disease risk or the p-globin gene and sickle cell anemia, researchers have found that when using SNP (single nucleotide polymorphism analysis) it was difficult to associate SNPs with disease states or to even identify key genes as being associated with disease (Pennisi, Science, 281 (5384):1787-1789). Finally, in some cases where multiple polymorphisms are identified in a gene, some of these are demonstrated to be disease associated and some are not. Blumenfeld et al. (WO 99/52942) disclose a number of polymorphisms in the FLAP gene. While Blumenfeld et al. were able to demonstrate that some of these polymorphisms are associated with patients having asthma but some of these are not (see Figure 3). For example, the marker 10-35/390 was demonstrated to be associated with asthma, with a p value of 0.00229, while the marker 10-33/327 was determined to not have a statistical association with asthma (p=0.294). Thus, even for SNPs within the same gene, it is highly unpredictable as to whether a particular marker will be disease associated.

Determining how to use the claimed polynucleotides as asserted by applicant, for example for the diagnosis of disease, requires the knowledge of unpredictable and potentially non-existent associations between the polymorphism and some periodontal disease or other disease state. Even if the elected polymorphism is in some way associated with some disease state, it is difficult (if not impossible) to know or predict from the teachings of the specification which disease or how the polymorphism(and what polymorphism) is associated. That is, it is unpredictable as to whether the presence of a particular allele the polymorphism would confer a higher or lower likelihood of having the disease. In this case, the possible uses for the claimed methods are undefined, beyond the suggestion that they can be used to detect a disease associated with the polymorphism.

Number of working examples and Guidance provided by applicant. The instant specification only provides guidance and working examples concerning the FcγRI, RIIA, RIIIA,

and RIIIB IgG receptor molecules. Considering the unpredictability surrounding the extrapolation of data from experiments using different receptor molecules, as pointed out in the Nature of the invention section of this rejection, the skilled artisan would have to practice undue and unpredictable trial and error experimentation in order to practice the invention with the genotypes of IgA receptors(FcαRI) that are not the genotypes of IgG receptors(FcγRI..etc.). In addition, considering the lack of working examples showing the association between a particular SNP and a specific disease, even more unpredictability exists.

Level of skill in the art. The level of skill involved in relating characteristics of such different molecules(FcαRI and FcγRI etc) to each other is very high if not impossible. Additionally, the functional use of such assumed similar properties from such different molecules is seen, in this instance, to be prophetic.

Unpredictability of the art. There are examples of differences in the IgG receptor and that being claimed, the IgA as illustrated in the State of the Art section. Both the prior art and the instant specification are deficient in terms of teaching the applicability of IgG receptor data to that of IgA genotype effects. Furthermore, the lack of teachings of how to use any genotype selected from the group consisting of 87R/87R, FcαRIA 92D/92N, FcαRIa 132F/132L, FcαRI 245P/245L and FcαRI 248S/248G of the FcαRI gene, and also how the actual induced function actually relates to this genotype both contribute to the great unpredictability involved in making and using this invention. In light of these deficiencies, the skilled artisan would be forced to practice undue and unpredictable trial and error experimentation when practicing the instant invention.

Considering the Nature of the invention, the guidance provided by both the prior art and the instant specification, and the broad scope of the invention, it is clear that the skilled artisan would be required to practice undue and unpredictable trial and error experimentation to practice the invention that is claimed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sally A Sakelaris whose telephone number is 571-272-0748. The examiner can normally be reached on M-Fri, 9-6:30 1st Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones can be reached on 571-272-0745. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Sally Sakelaris
12/16/2004

JEFFREY FREDMAN
PRIMARY EXAMINER
12/15/04